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KRIKORIAN, J	
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DATE MAILED: 05/17/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1/17/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-26 are pending in the application.
   Of the above, claims 1-5 + 21-25 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 6-20 + 26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

☐ Other

EXAMINER'S ACTION

12 May 1995

15. Applicants elected with traverse Group II, claims 6-20, Species A (basal cell carcinoma), claims 6 and 16, in Paper No. 16. The restriction was made final in the previous Office Action. Claims 6-20 were rejected in the previous Office Action. Applicants amended claims 6, 8, and 10-20, and added new claim 26 in Paper No. 19. Accordingly, claims 6-20 and 26 are under consideration, with the elected species basal cell carcinoma being examined. The amendments to the Abstract have been entered.

16. The disclosure is objected to because of the following informalities:

A. The Abstract of the Disclosure is objected to because it a single, incomplete sentence, and because it does not describe the invention. The abstract currently states that the invention is drawn to the treatment of several nonelected diseases and to a composition. The instant invention is drawn to a method for treating a disease or condition comprising basal cell carcinoma. Correction is required. See M.P.E.P. § 608.01(b).

B. Applicant is reminded of the proper content of an Abstract of the Disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative. The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art. Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

C. Applicant is reminded of the proper language and format of an Abstract of the Disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said", should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," *etc.*

D. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction of these and all other similar errors is required.

17. Receipt of the corrected oath or declaration filed 5 March 1993 claiming priority to application Serial No. 07/675,908 and to Canadian application Serial No. 2,061,566 is acknowledged. However, the oath or declarations are defective because they do not state whether each inventor is a sole or joint inventor of the invention claimed. It is suggested that a single oath or declaration be filed which identifies each inventor as sole or joint. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

18. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

19. This application contains several incomplete literature citations (e.g., page 10, lines 21 and 22, and page 12, line 15). Applicant is requested to provide the complete citation information of nonpatent references cited, including the date of publication, publication name, volume number, page numbers, and if a book, the publisher name and place of publication.

REJECTIONS WITHDRAWN

20. The rejection made under U.S.C. § 101, for the reasons set forth in Items 16 and 17 of the previous Office Action, is withdrawn.

21. The rejection of claims 11, 15, and 20 under U.S.C. § 112, second paragraph, for the reasons set forth in Item 19 of the previous Office Action, is withdrawn.

22. The rejection of claims 6-20 under U.S.C. § 103 for the reasons set forth in Item 20 of the previous Office Action is withdrawn.

REJECTIONS

23. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

A. Claims 6-20 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: (i) the dosage range of "50-60 mg" of hyaluronic acid recited in claim 6 is not disclosed in the specification as filed; (ii) the concentrations of components 1 (drug) and 2 (hyaluronic acid) as recited in claims 11 and 12 are expressed in terms of a percentage of the dosage amount, yet the formulations disclosed in the specification as filed (e.g., pp. 28 and 34-43) describe the amount of drug and hyaluronic acid as a percent of the total composition, and not as a portion of the **dosage** amount. Further, the specification as originally filed does not disclose a dosage amount of hyaluronic acid exceeding a concentration of 1½%, with no

upper limit, or is less than 3%, with no lower limit, as claimed in claim 11, or where the dosage amount of component 1 (i.e., the drug) exceeds a concentration of 1%, with no upper limit, or is less than 5%, with no lower limit, as claimed in claim 11.

B. The specification is objected to and claims 6-20 and 26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or unpredictability of the art, (4) the relative skill of those skilled in the art, (5) the amount of direction or guidance presented, (6) the quantity of experimentation necessary, and (7) the breadth of the claims. In evaluating the facts of the instant case, the following is noted:

(1) The nature of the invention is the treatment of a disease or condition of the skin, comprising basal cell carcinoma, in a mammal, comprising the topical administration of a pharmaceutical composition comprising a drug which inhibits prostaglandin synthesis and hyaluronic acid. The object or endpoint of the treatment is not recited in the claims. It is likely that remedies for the diseases or disorders *per se* does not presently exist.

(2 The state of the prior art was that there was no known "cure" for basal cell carcinoma. However, spontaneous remission is known to occur in the absence of medical or surgical intervention. Note Kelley *et al.* (1990). Applicants background description discloses that basal cell carcinoma is presently treated by surgery.

(3) The art of pharmaceutical treatments for human diseases and disorders is relatively unpredictable. In the instant case, the composition used for the method comprises an NSAID and HA. NSAIDS are a known class of pharmaceuticals and have been used in humans for years. What function is attributed to HA in the claimed composition and method is unclear; thus the predictability or unpredictability of its function in the method cannot be assessed.

(4) The relative skill of those in the art of cancer treatment is commonly recognized as being high in the field of pharmaceutical treatments in biotechnology, that is, a person with a medical (or similar) degree.

(5) The amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation. In particular, the specification lacks adequate guidance as to what dosage of a particular molecular weight of hyaluronic acid and prostaglandin inhibitor to administer topically to treat basal cell carcinoma. The specification describes the administration of hyaluronic acid with diclofenac in four individuals with basal cell carcinoma of the skin (pp. 53-55). The examples refer to formulations, but not to specific dosages administered. In addition, the frequency and duration of drug administration appears to be different for each patient, and the dosage schedule is not completely described for each individual. Thus, it is unclear what dosage of each component of the composition and what schedule is required to carry out the method. It is further noted that the examples provided were uncontrolled studies. Thus, although applicant concludes that the disappearance of lesions was due to the treatment, the reasons for this conclusion are unclear. As noted above, the art recognized that basal cell carcinomas can disappear spontaneously. Thus, it is unclear if the results are anecdotal or random, which would not be unexpected, or if they were a result of the treatment.

(6) The quantity of experimentation necessary needed to practice the method would be undue, in view of the inadequate guidance or direction provided, as indicated above. Thus, it would require undue experimentation by one of ordinary skill in the art to determine how to carry out the method claimed. See *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). It is further noted that the specification lacks direction as to what dosage(s) of hyaluronic acid are needed to carry out the method of treatment as claimed. Although formulations are described, the doses administered to the patients are not. Applicants have provided no teaching or guidance indicating what dosages are required to "resolve" or cause to disappear the basal cell carcinoma. It is further noted that the hyaluronic acid used for the Formulations 1 and 2 used in the examples (described at pages 53-55) to treat basal cell carcinoma had a molecular weight of 661,660 daltons or 679,000 daltons. The amount of hyaluronic acid to use when the hyaluronic acid has a different molecular weight from that noted (which is encompassed by the claims) is not disclosed, and no guidance is provided for determining the amount. Thus, it would require undue experimentation of one of ordinary skill in the art to determine how to carry out the method claimed.

(7) The breadth of the claims encompasses the method using any prostaglandin inhibitor and hyaluronic acid. In the examples provided, the prostaglandin inhibitor used was

diclofenac. While inhibition of prostaglandin synthesis may be one property of diclofenac, there is no evidence of record to suggest that inhibition of prostaglandin is the property that is relied upon or critical to make the composition useful for the method. Reynolds *et al.* teach that NSAIDS have multiple pharmacological properties, such as anti-inflammatory, analgesic, and anti-pyretic activities, as well as the inhibition of prostaglandin synthesis (p. 234, col. 1). Further, there is no evidence of record that hylauronic acid inhibits prostaglandin synthesis. Thus, the specification lacks support for the use of any prostaglandin inhibitor in a composition with hyaluronic acid for the treatment of basal cell carcinoma.

As noted in the previous Office Action, the claimed subject matter also encompasses fragments and subunits of hyaluronic acid (HA) (e.g., note claims 6 and 8), HA within the broad range of having a molecular weight of less than 750,000 daltons (e.g., note claims 8 and 12). It is unclear if the fragments and subunits, or any HA having a molecular weight of less than 750,000 daltons, have the same functional activity as the 661,660 daltons and 679,000 dalton hyaluronic acid and that would make them useful for the method claimed. No working examples are provided for the method using fragments or subunits of hyaluronic acid, or for HA having a molecular weight of less than 750,000 daltons. West *et al.* (1989) teach that high molecular weight HA has different functional properties in tissues from low molecular weight HA. For example, West *et al.* teach that *in vivo* studies indicate that a hyaluronate-rich stroma inhibits blood vessel formation in chick limb buds, whereas low molecular weight oligosaccharides of HA stimulate angiogenesis *in vivo* and endothelial cell proliferation *in vitro* (e.g., p. 179, abstract, p. 180, first paragraph, and p. 195). West *et al.* suggest that this finding is an important consideration for tumor growth, since tumor growth depends on angiogenesis. Thus, since it is apparent from West *et al.* that low molecular weight HA may in fact promote the growth of tumors, clearly low molecular weight HA would not have properties that make it useful for the method claimed.

In their response, applicants argue that fragments and subunits of HA are the same as HA. Assuming *arguendo* that this is the case, then the fragments and subunits need not be recited separately from HA. However, as noted, *supra*, low molecular weight HA does not have the same properties as the larger polymer. Thus, fragments and subunits as broadly claimed would not be expected to have the same properties as larger molecular weight or intact HA.

It is further noted that a dose of HA of "at least 50-60 mg" broadly encompasses any amount greater than 60 mg. The amount actually administered to patients with basal cell carcinoma is not disclosed in the specification. Thus, the 50-60 mg dosage and the broad range encompassed are not originally described or enabled. Further, the various embodiments of the composition recited in claims 11-20 and 26 broadly encompass very high and very low doses of drug and HA (including zero), which is not enabled by the specification as filed. Extremely low concentrations of drug or HA would not be expected to perform the method claimed, by applicants admission that at least HA must be in high doses. Extremely high doses of drug or HA have not been tested. HA in particular is known to be highly viscous (especially the high molecular weight form), and would not be expected to penetrate the skin at extremely high concentrations. Though not controlling, the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases his conclusions on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the Examiner may, properly, ask for evidence to substantiate them.

C. The effective amount and therapeutically effective amount of the drug and HA as claimed is not adequately described, since the object of "treat and resolve" is unclear. That is, one would not know if the object of the method is to reduce the inflammation of the lesions, or to cause the lesions to completely disappear without recurrence, for example. The claims do not recite what particular property or function is achieved by the method. Thus, the "effective amount" and "therapeutically effective amount" cannot be determined because one would not know for what the amount is effective. Similarly, a person skilled in the art would not known what is a "nontoxic" amount of drug or HA. The specification also lacks guidance as to what amount of drug and HA is toxic or nontoxic. Further, the amount of a drug or HA that may be toxic depends on the tissue and what particular changes or properties constitute toxicity. Thus, without adequate direction, a person skilled in the art would not know how to determine an effective amount, or a pharmaceutically effective amount.

24. Claims 6-20 and 26 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

25. Claims 6-20 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 6 is vague and indefinite in the recitation of the steps for the method. The claim does not recite a step where the composition is applied to the site of the basal cell carcinoma lesion.

B. Claim 8 and 12 are vague and indefinite in the recitation of the molecular weight of HA. The method by which said molecular weight is determined are not recited. It is well known that the apparent molecular weight of a molecule varies, depending on the method used to make the determination.

C. Claim 10 is vague and indefinite because it is in improper Markush form in the recitation of the various drugs.

D. Claim 11 is vague and indefinite because it is in improper Markush form in the recitation of the various embodiments of the composition (i-x).

E. Claim 6 is vague and indefinite in the use of parentheses. It is unclear whether or not the phrases presented in parentheses as recited represent claim limitations.

F. Claims 6, 8, are vague and indefinite in the recitation of "and/or". The repeated use of the term renders unclear and indefinite the particular subject matter being claimed. The term does not distinctly point out the claimed subject matter, since it refers to the items in the claims in both the alternative (or) and in the collective (and).

G. Claim 9 is vague and indefinite since it lacks antecedent basis in the claim from which it depends (claim 8) for the term "the drug".

26. Claim 10 contains several drug names which may be trademarks or trade names. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The scope of the claims is uncertain since the trademark or trade name cannot be used properly to identify a particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or

trade name. In the present case, the trademark or trade name is used to identify or describe an NSAID and, accordingly, the identification or description is indefinite.

The use of the trademarks have been noted in the specification. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permitted in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

27. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

28. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

29. Claims 6-20 and 26 are rejected under 35 U.S.C. § 103 as being unpatentable over Della Valle *et al.* (U.S. Patent No. 4,376,024), in view of applicants' admission of the prior art and Schultz *et al.* (U.S. Patent No. 4,808,576). Briefly, claim 6 is drawn to a method for treating a disease or condition of the skin, comprising basal cell carcinoma, in a mammal, comprising the topical

administration of a pharmaceutical composition comprising a drug which inhibits prostaglandin synthesis and at least 50-60 mg of hyaluronic acid (HA). The claim is being read as being limited to a method for treating basal cell carcinoma. The amount of HA administered is at least 50-60 mg. Claim 7 limits the method of claim 6 to daily administration for a number of weeks. Claim 8 limits the HA of claim 6 to having a molecular weight of less than 750,000 daltons. Claim 9 limits the method of claim 8 to wherein the drug is an NSAID. Claim 10 further limits the NSAID of claim 9 to an NSAID selected from (the group consisting of) diclofenac, indomethacin, naproxen, (+/-) tromethamine salt of ketorolac, ibuprofen, piroxicam, proprionic acid derivatives, acetylsalicylic acid, and Flunixin. Claims 11-20 and 26 limit the method to one of ten various embodiments of the composition, where the concentrations of HA and drug vary. Claim 12 further limits the HA of claim 11 to having a molecular weight of less than 750,000 daltons. It is noted that since the method of claim 6 recites treating a disease **comprising** (the step of) the topical administration of a composition, that the method is not limited to that particular step.

Della Valle *et al.* teach (i) that pharmaceutical compositions comprising HA and a pharmacological substance that are useful for topical application, especially in dermatology (e.g., col. 1, lines 11-33 and claim 11); (ii) that HA is a more efficient vehicle than other reagents for the bioavailability of active drugs (col. 1 , lines 34-41); (iii) that the pharmacologic substance may be a non-steroidal anti-inflammatory drug, such as indomethacin (e.g., col. 4, lines 26-28), an anti-tumor agent (col. 4, line 19), or a cytostatic agent (col. 4, line 47); (iv) that the HA has a molecular weight of from about 30,000 to about 13 million, with the range of 30,000 to 730,000 being preferred (e.g., col. 6, lines 33-48); (v) that the HA may be a pharmaceutically acceptable salt of HA (e.g., col.7, lines 34-62 and col. 8, lines 24-44); and (vi) that the composition is provided in a pharmaceutically-acceptable carrier, such as sterile saline (e.g., col. 8, line 63 to col. 9, line 31). The ratios (by weight) of drug and HA may be in the range of 0.001:1 to 100:1 (drug:HA), with the preferable range being between 0.01:1 and 10:1 (col. 8, lines 48-57). This range is with the ranges of drug and HA recited in claims 11-20 and 26. It is noted that non-steroidal anti-inflammatory drugs (NSAIDS) such as indomethacin were known and used at the time to inhibit prostaglandin synthesis and to reduce pain. By definition, NSAIDS also reduce inflammation, which was known at the time. Effective doses and LD_{50} of common NSAIDS, such as those recited, were also known at the time, so that a determination of and administration of a nontoxic dose would have been routine. Although Della

Valle *et al.* teach that the composition is useful for dermatologic uses and includes the use of anti-tumor and cytostatic agents in the composition which suggest the use of the composition in treating cancers of the skin, Della Valle *et al.* do not teach a method for treating basal cell carcinoma *per se*, or a dose of HA of at least 50-60 mg.

However, applicants admit at page 1 of the specification that basal cell carcinoma was known at the time to be treated by surgical removal of the lesions. It has been recognized for centuries that the site of surgery in general is associated with postoperative pain and inflammation. Schultz *et al.* teach the administration of HA to mammals to reduce pain and swelling of traumatized tissue (e.g., paragraph bridging cols. 2 and 3), wherein the HA may be applied topically, and is administered at a dose of between 0.02 to 0.15 mg per pound of body weight (col. 5, line 49-col. 6, line 18). Thus, for a 500-lb. mammal, the dose may be 75 mg,which is within the dose range recited in the claims.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine (i) the teachings of Della Valle *et al.* as to the known benefits of using a composition comprising HA having a molecular weight of less than 750,000 (including that HA is a more efficient vehicle than other agents) with an NSAID in nontoxic amounts in the topical application of the composition to the skin; (ii) the known properties of NSAIDs of inhibiting prostaglandin synthesis and reducing pain and inflammation; (iii) the teachings of Schultz *et al.* as to the known property and use of HA to reduce pain and swelling of traumatized tissue and to use high doses of HA for topical treatment (such as 60 mg/400 lb. body weight); (iv) applicants' admission that basal cell carcinoma was known and treated by surgery; and (v) the known postoperative side effects of surgery of pain and inflammation, for the benefit of reducing postsurgical pain and inflammation as a step in the treatment of basal cell carcinoma by applying a composition comprising HA and an NSAID to the site after surgical removal of the lesion, as a step in the treatment of the carcinoma. As noted above, since the method of claim 6 recites treating a disease **comprising** (the step of) the topical administration of a composition, the method is not limited to that particular step. Accordingly, claims 6-20 and 26 are *prima facie* obvious over the prior art, absent sufficient objective factual evidence to the contrary.

30. In response to the rejection made under 35 U.S.C. § 103 in the previous Office Action, applicants have presented arguments which may apply to the above rejection, even though the previous

rejection has been withdrawn. Applicants comments are briefly addressed here were they are relevant to the new rejection. First, applicants assert that the previous rejection did not contain a motivation for combining the references. The motivation for combining references is clearly set forth in the rejection, *supra*. In particular, and for applicants' benefit, the motivation is "for the benefit of reducing postsurgical pain and inflammation as a step in the treatment of basal cell carcinoma by applying a composition comprising HA and an NSAID to the site after surgical removal of the lesion, as a step in the treatment of the carcinoma". The elements leading one to this reason were set out in the references, or were generally known in the art, as noted, *supra*. Second, applicants argue that the combination of references was made by hindsight. However, in the present situation, this argument is made moot since a motivation has been clearly established and set forth. Third, applicants argue that the specific embodiments of the claimed subject matter were not taught by the references in the previous rejection. Applicant has not pointed out the particular claim limitations that were not addressed. However, with respect to the new rejection, *supra*, all of the limitations carrying patentable weight have been addressed. Fourth, applicants addressed the specific teachings of the references applied in the previous Office Action. With respect to the references applied in the rejection made herein, applicants argue that Della Valle *et al.* (U.S. Patent No. 4,736,024) does not teach HA at the dosage amounts claimed. However, the dosage amounts claimed are taught by Schultz *et al.*, who also administered HA, as noted *supra*. Applicants further argue that Della Valle teach that the HA applied to the eye acts as a "depot". The location of this particular language in the reference is not apparent. Nevertheless, and as noted, *supra*, the reference clearly teaches the topical application of a composition comprising HA and a drug for dermatological use (i.e., to the skin). There is no teaching that the HA is not absorbed into the skin. Rather, Della Valle *et al.* teach that HA acts as a more efficient vehicle for drug bioavailablilty. Further, even if the HA of Della Valle *et al.* acts as a depot, it is unclear how this relates to the nonobviousness of the claimed invention. Since the HA of Della Valle *et al.* appears to be identical to the HA of the instant invention, it would have the same inherent physical and biological properties. The comments of applicatns regarding Schultz *et al.* are not understood. Schultz *et al.* teach the topical administration of HA compositions to treat pain and inflammation at a dose that is encompassed by the instant claims. Whether the HA is a carrier or is active is moot since the claims do not limit the HA to having a particular mechanism of action. Applicants remaining arguments concern art that is no longer being applied.

31. Claims 6-20 and 26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-216, 218-244, 249-272, and 275-346 of copending application Serial No. 07/675,908, claims 1-71 of copending application Serial No. 08/018,754, and claims 35-41, 47-51, 57, and 58 of copending application Serial No. 08/018,508. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to a method for treating a disease or condition, including cancer, comprising administering a composition comprising hyaluronic acid and a drug, wherein the drug may be an NSAID, and a composition for use in the methods. The composition and methods of the copending application use the same composition in the treatment of cancer, such as skin cancer. As noted previously, basal cell carcinoma, recited in the instant application, is a form of skin cancer. The choice of the particular molecular weight of HA, dose, and topical application would have been routine at the time. This is a *provisional* obviousness-type double patenting rejection.

32. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

33. It is noted that the inventorship in copending application Serial Nos. 07/675,908 and 08/018,508 is the same as that in the instant application. However, the inventors of application Serial No. 08/018,754, are Falk, Asculai, Klein, Harper, Hochman, and Purschke. Application Serial No. 08/018,754 is a CIP of application Serial No. 07/675,908, filed 7/3/91.

34. Claims 6-20 and 26 are directed to an invention not patentably distinct from claims 1-216, 218-244, 249-272, and 275-346 of copending application Serial No. 07/675,908, claims 1-71 of copending application Serial No. 08/018,754, and claims 35-41, 47-51, 57, and 58 of copending application Serial No. 08/018,508. Commonly assigned Serial No. 07/675,908, Serial No.

08/018,754, and Serial No. 08/018,508, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Reynolds (1982) teaches the properties of NSAIDS in general, and of specific NSAIDS in particular. The general properties include inhibition of prostaglandin synthesis and analgesic properties (p. 234, col. 1). Alho *et al.* (1989) teach that the hyaluronate receptor is preferentially expressed on proliferating epithelial cells, and that the hyaluronate receptor is present in tumor cells, and may serve as a marker for tumor cells.

36. Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The appropriate Group 1800 facsimile telephone numbers for this art unit are (703) 305-7362 and (703) 305-7401.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Krikorian whose telephone number is (703) 308-3964. Dr. Krikorian may normally be reached from 8:30 AM to 4:00 PM, Monday through Thursday and on alternate Fridays. If attempts to reach the Examiner by telephone are unsuccessful, Supervisory Patent Examiner Ms. Margaret Moskowitz Parr may be reached at (703) 308-2454.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

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